

General

Guideline Title

Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2012 Mar 27;78(13):1009-15. [36 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Guillain-Barré Syndrome

Conclusions

1. Based on conflicting primary outcome measures, IV immunoglobulin (IVIg) benefit is uncertain in children with Guillain-Barré syndrome (GBS).
2. Based on 2 Class I studies, IVIg is as efficacious as plasmapheresis for treating GBS in adults. Because plasmapheresis is established as effective GBS treatment, the guideline committee concluded that IVIg also has established effectiveness.
3. Based on one adequately powered Class I study, the combination of plasmapheresis and IVIg is probably not better than either treatment alone.
4. Based on one underpowered Class I study, evidence is insufficient to support or exclude a benefit of adding methylprednisolone (MP) to IVIg in GBS.
5. Data are insufficient to make a recommendation on optimal IVIg dosing.

Recommendations

There is insufficient evidence to support or refute the effectiveness of IVIg in children with GBS (Level U).

IVIg should be offered to treat GBS in adults (Level A).

IVIg combined with plasmapheresis should not be considered for treating GBS (Level B).

Evidence is insufficient to recommend MP in combination with IVIg (Level U).

Clinical Context

Many experts consider it reasonable treatment to use IVIg for GBS in children given its effectiveness in the same disease in adults.

Chronic Inflammatory Demyelinating Polyneuropathy

Conclusions

1. Based on 2 Class I studies, IVIg is effective for the long-term treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).
2. Data are insufficient to address the comparative efficacy of prednisolone and IVIg in treating CIDP.

Recommendation

IVIg should be offered for the long-term treatment of CIDP (Level A).

Clinical Context

Dosing, frequency, and duration of IVIg for CIDP may vary depending on the clinical assessment. Data are insufficient to address the comparative efficacy of other CIDP treatments (e.g., steroids, plasmapheresis, immunosuppressants). Experts have identified that there may be overuse of IVIg in long-term care of CIDP. The guideline committee was unable to evaluate this question using available randomized trial data.

Myasthenia Gravis

Conclusions

1. Based on one Class I study, IVIg is probably effective in treating patients with myasthenia gravis (MG).
2. Evidence is insufficient to compare the efficacy of IVIg and plasmapheresis in treating MG.

Recommendation

IVIg should be considered in the treatment of MG (Level B).

Clinical Context

This recommendation was based on studies involving primarily moderately or severely affected patients. The benefits and risks of this medication should be weighed carefully in patients with mild MG. Further studies of IVIg efficacy in MG are warranted due to the few randomized trials and small study size to date.

Multifocal Motor Neuropathy

Conclusion

Based on consistent results from 3 Class II studies, IVIg is probably effective for multifocal motor neuropathy (MMN) treatment.

Recommendation

IVIg should be considered for the treatment of MMN (Level B).

Clinical Context

MMN is a chronic disease requiring ongoing treatment. No data are available to address optimal treatment dosing, interval, and duration.

Neuropathy Associated with IgM Paraprotein

Conclusion

Based on 1 Class I study and 1 Class II study, IVIg is possibly ineffective for the treatment of IgM paraprotein-associated neuropathy. A modest benefit cannot be excluded due to each study's small sample size.

Recommendation

Evidence is insufficient to assess the role of IVIg in treating neuropathy associated with IgM paraprotein (Level U).

Dermatomyositis

Conclusion

Based on 1 Class II study, IVIg is possibly effective for the treatment of nonresponsive dermatomyositis in adults.

Recommendation

IVIg may be considered for the treatment of nonresponsive dermatomyositis in adults (Level C).

Inclusion Body Myositis

Conclusion

Two Class I studies and 1 Class II study failed to demonstrate a consistent or significant clinical benefit of IVIg in treating inclusion body myositis (IBM).

Recommendation

Evidence is insufficient to support or refute the use of IVIg in treating IBM (Level U).

Clinical Context

There is presently no effective treatment for IBM.

Postpolio Syndrome

Conclusion

One Class I study showed a significant difference, but the difference was not clinically important for IVIg use on the most affected muscle in postpolio syndrome. One underpowered Class I study showed an effect of IVIg for pain in postpolio syndrome but no effect on strength or fatigue.

Recommendation

Evidence is insufficient to support or refute IVIg use in the routine treatment of postpolio syndrome (Level U).

Clinical Context

There is presently no effective treatment for postpolio syndrome.

Lambert-Eaton Myasthenic Syndrome

Conclusion

Based on 1 Class II study, IVIg is possibly effective in Lambert-Eaton myasthenic syndrome (LEMS).

Recommendation

IVIg may be considered in the treatment of LEMS (Level C).

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Evidence for Rating of a Therapeutic Article

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Neuromuscular disorders including:

- Guillain-Barré syndrome (GBS)

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Myasthenia gravis (MG)
- Multifocal motor neuropathy (MMN)
- Neuropathy associated with immunoglobulin M (IgM) paraprotein
- Dermatomyositis
- Diabetic neuropathy
- Miller Fisher syndrome
- Inclusion body myositis (IBM)
- Postpolio syndrome
- Lambert-Eaton myasthenic syndrome (LEMS)

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Pediatrics

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the evidence for the efficacy of intravenous immunoglobulin (IVIg) to treat neuromuscular disorders

Target Population

Patients with neuromuscular disorders

Interventions and Practices Considered

Intravenous immunoglobulin (IVIg)

Major Outcomes Considered

- Disability
- Intervals from onset to maximum weakness to improvement

- Hospitalization length
- Quantitative muscle strength
- Pain
- Improvement in cytoarchitecture and reduced muscle inflammation as measured by muscle biopsy
- Disability improvement from baseline as measured by:
 - Inflammatory Neuropathy Cause and Treatment Score (INCAT)
 - Medical Research Council (MRC) scale
 - Quantitative Myasthenia Gravis (QMG) score
 - Modified neurologic disability scale (NDS)
- Activities of daily living scores based on Barthel Index
- Improved quality of life as measured by the Short Form-36
- Vital capacity
- Drinking time
- Antibody titer
- Rash
- Adverse effects

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A literature search of MEDLINE, Web of Science, and EMBASE databases from 1966 to 2009 was conducted, using the search term "immunoglobulin" and one of the following: myasthenia gravis, Guillain-Barré syndrome (GBS), neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, polymyositis, dermatomyositis, diabetic neuropathy, diabetic radiculoplexoneuropathy, postpolio syndrome, paraproteinemic neuropathy, Lambert-Eaton myasthenic syndrome, Miller Fisher syndrome, inclusion body myositis.

At least 2 panelists reviewed each abstract result; articles were included if they were therapeutic studies relevant to the efficacy, safety, tolerability, or intravenous immunoglobulin (IVIg) mode of use in humans. Reviews and meta-analyses were reviewed to ensure inclusion of all relevant published studies.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Rating of a Therapeutic Article

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

- a. Concealed allocation

- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 - 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 - 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 - 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 - 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Studies were rated according to the American Academy of Neurology (AAN) therapeutic classification of evidence scheme (see the "Rating Scheme for the Strength of the Evidence" field). Disagreements on article classification were resolved by discussion.

All data analyzed are presented in tables e-1 to e-14 of the original guideline document appendices.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Therapeutics and Technology Assessment subcommittee selected panelists on the basis of expertise in intravenous immunoglobulin (IVIg) use or familiarity with the guideline process, or both.

Recommendations were linked to the strength of the evidence (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, *Neurology*® peer reviewers and representatives from related fields. The guideline was approved by the Therapeutics and Technology Assessment Subcommittee on January 3, 2011; by the Practice Committee on February 7, 2011; and by the AAN Board of Directors on December 12, 2011.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate IV immunoglobulin treatment of neuromuscular disorders which can reduce disability

Potential Harms

Most studies concluded that IV immunoglobulin (IVIg) was well-tolerated and adverse effects were either transient or manageable. Serious adverse effects related to IVIg were rare and included aseptic meningitis, urticaria, heart failure, myocardial infarction, and renal failure. These

findings do not exclude the possibility of rare adverse effects such as stroke and thrombotic events, which have been previously reported with IVIg. It is important to screen for vascular risk factors before infusion and to monitor carefully during and after infusion. The most common IVIg-related adverse effects included headache (16.1%), fever (6.6%), mild hypertension (4.6%), chills (3.3%), nausea (3.2%), asthenia (1.4%), arthralgia (1.3%), anorexia (1.1%), dizziness (1.1%), malaise (1.1%), and transient hyperglycemia (1.1%).

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guidelines into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Mar 27

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology

Guideline Committee

Therapeutics and Technology Assessment Subcommittee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Conflict of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*® peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at [American Academy of Neurology website](#) .

Disclosure

Dr. Patwa was an investigator in the ICE trial comparing IVIg with placebo for CIDP. Dr. Chaudhry serves on the editorial board of *Neurologist*; is an inventor on patent(s) re: Total Neuropathy Score (TNS)—a score for evaluating peripheral neuropathies, for which he receives technology royalties from Abbott, Johnson & Johnson, and sanofi-aventis; receives publishing royalties for *Harrison's Principles of Internal Medicine, 17th ed*, (McGraw Hill Companies, Inc., 2008); estimates that 40% of his clinical effort is spent on nerve conduction studies; has given expert testimony for the Department of Health and Human Services Vaccine Injury Compensation program; and receives research support from the Neuropathy Association, Nutricia, and Inmed Inc. Dr. Katzberg has received funding for travel from the Muscular Dystrophy Association. Dr. Rae-Grant has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., and EMD Serono, Inc.; receives publishing royalties for *Handbook of Multiple Sclerosis* (Springer Healthcare, 2010); and has served on the speakers' bureau for Biogen Idec. Dr. So receives publishing royalties for *Occupational & Environmental Medicine* (Appleton & Lange, 2007), and contributions to UpToDate; receives research support from the NIH (NIEHS, NINDS); and holds stock in Sartoris, Inc.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the [AAN Web site](#) .

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

Availability of Companion Documents

The following are available:

- Evidence-based guideline: IV immunoglobulin in the treatment of neuromuscular disorders. Data supplement (e-appendices, e-tables). Available from the [American Academy of Neurology \(AAN\) Web site](#) .
- IV immunoglobulin in the treatment of neuromuscular disorders. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2012. 2 p. Available in Portable Document Format (PDF) from the [AAN Web site](#) .
- IV immunoglobulin in the treatment of neuromuscular disorders. Case presentation. St. Paul (MN): American Academy of Neurology. 2012. 6 p. Available in PDF from the [AAN Web site](#) .
- IV immunoglobulin in the treatment of neuromuscular disorders. Slide presentation. St. Paul (MN): American Academy of Neurology. 2012. Available from the [AAN Web site](#) .
- Evidence-based guidelines update: IV immunoglobulin in the treatment of neuromuscular disorders. CME course. Available online to subscribers of Neurology at the [Neurology Web site](#) .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the [American Academy of Neurology Web site](#) .

Patient Resources

The following is available:

- IV immunoglobulin for treating neuromuscular disorders. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology. 2012. 2 p. Available in Portable Document Format (PDF) from the [American Academy of Neurology \(AAN\) Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a

licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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